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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,555	12/08/2003	Katerina Heran Darwin	19603/4292 (CRF D-3099-03	3247

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EXAMINER
MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
1656	

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DATE MAILED: 04/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/730,555	DARWIN ET AL.	
	Examiner	Art Unit	
	William W. Moore	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 63-87* is/are pending in the application.

4a) Of the above claim(s) *7-11 and 69-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,12-20,63-68 and 74-87* is/are rejected.

7)☒ Claim(s) *3-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's Amendments in the Response filed 2 February 2006 have been entered, correcting obvious misspellings at pages 15 and 16 of the specification, canceling claims 21-62 and 88-102, and amending claims 1, 4, 63, 64, 77, 78, and 79-81. These Amendments introduce no new matter and overcome the objections of record to the specification. Rejections of record under the second paragraph of 35 U.S.C. § 112 of (i) claims 12-14 and 82-84 herein based on recitations of "oxidative/nitrosative stress", "reactive nitrogen intermediate" and "reactive oxygen intermediate", (ii) claims 3 and 65 herein based on the recitation of "proteasome core", and (iii) of claims 78 and 81 are WITHDRAWN in view of Applicant's claim amendments and Applicant's arguments in the Response. The rejections of record under the second paragraph of 35 U.S.C. § 112 of claims 1-6, 12-20, 63-68 and 74-87 based on the recitations of "conditions effective", of claims 4-6 based on the recitation "wherein the protease", as well as of claims 78-80 are also WITHDRAWN in view of Applicant's claim amendments. Other rejections of record of claims herein under the first and second paragraphs of 35 U.S.C. § 112 are, however, maintained for the reasons set forth below. Claims 1-20 and 63-87 remain herein, of which claims 7-11 and 69-73 are withdrawn from consideration as drawn to a non-elected invention.

Information Disclosure Statement

The information disclosure statement [IDS] filed 2 February 2006 need not comply with 37 CFR 1.97(c) because it was requested by the Examiner in the communication mailed 28 July 2005 and constitutes a correction of a citation made in the information disclosure statement filed 21 October 2004. The IDS is therefore ACCEPTED and is acknowledged in this communication. It is noted that Applicant submits fourteen further

publications, cited at pages 12-20 of Applicant's Response filed 2 February 2006, that had not yet been cited, and were not cited, in an IDS. The publications were considered and are made of record herewith on the accompanying PTO Forms-892.

Title and Abstract

The title of the invention remains objected to because it is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The title does not reflect the fundamental nature of the antibiotic therapy target of the claims elected for prosecution and examined herein where the restriction requirement was made Final in the communication mailed 28 July 2005: prokaryotic proteasomal proteases. The nature of the target for antibiotic therapy **must** be included in the Title.

The objection of record to the abstract of the disclosure is withdrawn in part and maintained in part. The genus of pathogens for which a claimed method of treatment is actually disclosed, Mycobacteria, must be included in the abstract.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 12-20, 63-68 and 74-87 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims remain drawn to methods of treating generic pathogens, save for claims 18 and 85, by inhibiting, at least in the case of claims 1, 2, 12-16, 18-20, 63-65, 74, and 76-87, generic "proteasomal activity" in the generic pathogen. Applicant's arguments filed 2 February 2006 have been fully considered but are persuasive only in part. Applicant suggests at pages 19 and 20 of the Response, that disclosure of the

resistance to unsustainable damage of its cellular proteins by *M. tuberculosis* exposed to reactive nitrogen intermediates and reactive oxygen intermediates produced by a host cell in the course of intracellular infection, and the susceptibility to such damage of mycobacterial strains with the genes encoding prokaryotic proteasomal components inactivated or disrupted, should be taken as evidence of the possession of methods of treating such infections. The specification's disclosure that infecting mammalian cells that are hosts for persistent mycobacterial infection with such genetically-manipulated strains results in eradication of the strains by host intracellular defense mechanisms is indeed considered to demonstrate a potential for treating such infections by applying external agents that impede internal processes of the prokaryotic proteasome. But the only method of treatment actually disclosed to be in Applicant's possession at the time the specification was filed is the method described by claims 3-6, no longer subject to the rejection of record. This is because using mycobacterial strains recombinantly impaired in the expression of effective proteasomal components to infect host cells, or animals, cannot be a method of treating an infection where the native pathogen having effective proteasomal components will supplant any defective strain administered to the host cell or animal and will persevere. The rejected claims thus lack adequate written description for methods of treatment requiring proteasomal and/or enzyme inhibitors that inhibit proteasomal and enzyme activity other than inhibitors of the proteases of the prokaryotic proteasome core.

"While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). Applicant declines to address the decision in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886,

(Fed. Cir. 2004), specifically pointing to the applicability of the earlier decisions in *Lilly* and *Enzo Biochemical* to claimed methods of using products, wherein said products lack adequate written description. The instant specification discloses only two classes of products, peptide boronates and peptide epoxyketones, that might be used to treat certain infectious diseases, mycobacterial infections, insofar as mycobacteria may persist as intracellular parasites while under attack by reactive nitrogen intermediates and reactive oxygen intermediates produced by a host cell. The decision in *University of Rochester v. G.D. Searle & Co.* addressed claimed methods held to lack written description where no example of a product to be used in a claimed method was described, thus is properly applied herein where only certain products are disclosed to be used for certain methods of treatment, but not others. The safety and efficacy of using the two disclosed kinds of protease inhibitor for treating tuberculosis or another disease caused by a mycobacterial pathogens where slow growth is the basis for their persistence to mount an active diseases state, while the publications Applicant cites at page 20 of the Response concern their promise in treating cancer by crippling the eukaryotic proteasomes of rapidly dividing cancer cells, is not at issue. The rejection of record is maintained because the scope of the claimed methods subject to this rejection far exceeds the disclosure.

Claims 1, 2, 12-20, 63-68 and 74-87 remain rejected for reasons of record under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for methods of treating mycobacterial infection by administering peptide boronate and peptide epoxyketone inhibitors of prokaryotic proteasomal core protease activity, does not reasonably provide enablement for methods of treating generic pathogen infections by inhibiting generic "proteasomal activity". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice a method of the invention commensurate in scope with these claims.

Applicant's arguments filed 2 February 2006 have been fully considered but are persuasive only in part. Claims 1, 2, 12-20, 63-68 and 74-87 contemplate the arbitrary administration of undisclosed agents or compounds in the treatment of infections by any

conceivable kind of pathogen – eukaryotic, prokaryotic, or viral – so long as the agent or compound inhibits some vague "proteasomal activity". Applicant suggests at page 20 of the Response that its summary of the disclosure indicates that one of ordinary skill in the art would have been able to "make and use the present invention". Neither the prior nor subsequent, publications in the relevant arts cited in the Response and made of record herewith can be combined with Applicant's specification to assist such an artisan in selecting further compounds or agents with which to treat infections by the myriad pathogens contemplated by the claims. Thus the rejection of record is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 12-20, 63, 64-68 and 74-87 remain rejected for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-6, 12-20, 63, 64-68 and 74-87 remain rejected because the phrase "treating pathogen infection . . . comprising inhibiting proteasomal activity" is indefinite. This rejection statement combines separate statements of the communication mailed 28 July 2005 because the issues are related. It is agreed that the specification discusses proteolytic activities within the proteasome cores of prokaryotic pathogens that can be inhibited, yet the term "pathogen" is ambiguous because some pathogens, e.g., viruses, have no proteasomes, and methods requiring inhibition of eukaryotic pathogens, the proteasomes of which do not differ from proteasomes of the disclosed subjects, also eukaryotes, cannot be considered to be a method of treatment. The term "proteasomal activity" is both vague and ambiguous where it need not be confined to an activity within the proteasome itself, or even occurring in the vicinity of a proteasome, when, e.g., the processing of proteins within cells that targets them for entry into a proteasome may also be construed to be a "proteasomal activity" particularly where any kind of cell may

be a "pathogen". The artisan and the public seeking to ascertain the metes and bounds of the intended subject matter cannot determine which are the pathogens to be treated or where a "proteasomal activity" begins or ends. Amending the preambles of claims 1 and 63 to state "treating bacterial pathogen infection" and amending the pertinent clauses of both claims 1 and 63 to state "inhibiting a protease activity of the proteasome core of a bacterial pathogen" would overcome this aspect of the rejection separately affecting both claims 4-6 and 64-68 and claims 1, 2, 12-20, 63, 64-68 and 74-87.

Claims 2-3 and 64-65 remain rejected because the term "proteasomal protease activity" in claims 2-3 and 64-65 is indefinite. The specification indeed discusses two protease activities within the prokaryotic proteasome core but the term "proteasomal protease activity" is not confined to such activity where any distant processing of proteins in cells to, e.g., prepare components to mark disused proteins for transit to proteasomes, may also be considered a "proteasomal protease activity". The artisan and the public seeking to ascertain the metes and bounds of the intended subject matter could not determine where a "proteasomal protease activity" to be inhibited begins or ends. The amendment proposed above would render claims 2, 3, 64, and 65 superfluous and they may be canceled to overcome this aspect of the rejection.

Claim 77 remains rejected because the phrase "group consisting of a DNA repair enzyme . . ." is indefinite. This cannot be a closed group where paragraphs 0049 and 0103 of the specification, the only discussions of a "DNA repair enzyme", indicate that it "includes, without limitation," a nucleotide excision repair enzyme yet provides no further hint of the unlimited nature of a generic "DNA repair enzyme". Nucleotide excision repair enzymes are themselves a genus including the prokaryotic *uvr*B gene products. The publications cited at page 15 of the Response cannot compensate for the uncertain direction in the specification because the artisan and the public seeking to ascertain the

metes and bounds of the intended subject matter could determine where an "activity" of DNA repair begins or ends. Claims 78-80 are no longer subject to this rejection in view of Applicant's amendments, thus amending claim 77 to replace the vague term "DNA repair enzyme" with "nucleotide repair enzyme", canceling claim 78, and amending claims 79 and 80 to depend from claim 77 would overcome this aspect of the rejection.

Conclusion

Claims 3-6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
6 April 2006

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER